2149-102
BGN

OIPE
JUN 24 2002
PATENT & TRADEMARK OFFICE
JC98

#7
RECEIVED
JUL 08 2002
TECH CENTER 1600/2900

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
Douglas H. ROBINSON	)	
	)	
Serial No. **08/719,367**	)	Examiner: J. Williams
	)	
Filed: September 25, 1996	)	Group Art Unit: 1815
	)	
For: METHODS FOR THE PRODUCTION OF BACTERIA CONTAINING EUKARYOTIC GENES	)	

DECLARATION OF ANTON STEUER, PH.D.

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Anton Steuer, Ph.D., declare as follows:

1. I am presently employed by MA Bioservices in Rockville, Maryland. I earned my Ph.D. degree in Cell Physiology from The Catholic University of America. I have particular expertise in the field of cell culturing techniques.

2. I personally supervised the work described in the attached Final Report -- "Evaluation of a Process for Generating Bacteria De Novo from Eukaryotic Cells." That report describes work performed at Microbiological Associates, Inc. ("MA") in 1996. At that time I was employed by MA as Director of the Biosafety Testing Division and Study Director for a variety of assays. Page 10 of the

Final Report identifies me as the "Study Director" and bears my signature.

3. The work described in the Final Report was commissioned by Dr. Robinson and was intended to provide independent repetition, under closely-monitored cell culturing conditions meeting rigorous Good Laboratory Practices (GLP) and Good Manufacturing Practices (GMP) standards, of work Dr. Robinson had performed in his own laboratory at Naval Medical Research Institute, Bethesda, Maryland. Dr. Robinson had previously observed the generation of bacteria when virally-infected eukaryotic cells (specifically, retrovirally-infected human brain capillary endothelial cells) were cultured under alternating anaerobic and aerobic conditions. Dr. Robinson approached MA and engaged MA to attempt to repeat his work as a means of independently reproducing his experiments to see whether bacteria again would be produced.

4. The work that was performed at MA is described in detail in the accompanying Final Report. As reported therein, culturing the virally-infected eukaryotic cells under alternating anaerobic/aerobic cell culture conditions produced bacteria. The cultures were sent to an outside company (Acculab, Inc.) that identified the colonies as B. licheniformis. The rigorous sterility testing performed upon the starting material and the rigorous procedures under

which the cells were aseptically cultured makes it highly unlikely that the bacteria were "contaminants."

5. I have read portions of an Office Action issued by the Patent and Trademark Office. The portions I read comments upon the attached Final Report, which I understand was previously submitted with a Declaration by Dr. Robinson. In paragraph no. 16, the Office Action states that the Final Report did not "rule out the possibility of bacterial contamination at each and every step of the claimed method." The Office Action therefor expresses the view that the results were due to contamination. I disagree with both that conclusion and the reasoning behind it that is presented in the Office Action.

6. I have many years of experience in the field of aseptic cell culturing techniques. The work performed in connection with Dr. Robinson's project used facilities, equipment and procedures that met or exceeded the most rigorous standards present in the industry -- both GLP and GMP standards. These same procedures have been used at MA for the evaluation of pharmaceutical products and biologicals destined for human use. My company's ability to provide aseptic material processing and accurate sterility test data is relied upon by its clients throughout the health care industry, including many of the world's largest pharmaceutical companies. Thus, it is clear to me that

people who are skilled and knowledgeable in this field of science have consistently relied upon my company's abilities to evaluate, handle and process materials while assuring a lack of contamination.

7. The Final Report provides extensive details regarding the specific sterility testing and aseptic cell culturing techniques that were employed. Additional verification of the quality of this work is provided on page 33 of the Final Report. There it is seen that MA's Quality Assurance department "signed-off" on the report, noting that the work complied with, among others, the U.S. FDA Good Laboratory Practice Regulations (21 CFR 58), the U.S. E.P.A. GLP's, the UK GLP Compliance Programme and the Japanese GLP Standard. The Quality Assurance department's inspection report is seen on that page.

8. It is my professional opinion that any scientific inquiry wherein one must "rule out" contamination, as set forth in the Office Action, is meaningless. Scientists skilled in this field do not "rule out" contamination. This is why the Final Report states that "the possibility of environmental contamination as the source of the bacterial isolates cannot be absolutely eliminated." For this same reason I worded my conclusion that contamination "was highly unlikely." No scientist skilled in this field would state that the possibility of contamination had been "absolutely

eliminated" or "ruled out" in any scientific procedure such as this. Rather, procedures are carried out under rigorously-controlled aseptic environments that minimize the possibility of contamination. The equipment, materials and procedures used at my company to test starting materials for contamination, to provide aseptic environments and to guard against contamination, and that were used in connection with Dr. Robinson's work, are recognized as meeting the highest quality standards. Thus, I conclude that the Patent Examiner has applied a requirement for "proving" a lack of contamination that is not applied by persons skilled in this field.

9. In paragraph 16 of the Office Action, the Patent Examiner has commented that "it is possible that the contaminants were intracellular bacteria and/or spores thereof which had not received the proper stimulus to grow and thus had evaded the detection means." It is my opinion that the rigorous sterility testing performed at MA in connection with this study makes this highly unlikely. Negative controls were run on the starting materials and throughout the study; all showed no bacterial outgrowths.

10. In conclusion, it is my professional opinion that the work reported in the attached Final Report was carried out using high quality techniques, materials and

facilities for sterility testing and cell culturing under aseptic conditions. It is my professional opinion that the B. licheniformis bacteria isolated as described in the Final Report did not originate as contaminants in the starting cell culture. Further it is my professional opinion that environmental contamination during the cell culturing processes is highly unlikely due to the procedures and practices employed in the performance of the study.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed at Rockville, Maryland, this 30th day of September, 1997.

Anton Steuer

Anton Steuer, Ph.D.